REMARKS

The Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the reasons that follow.

I. Substance of the Interviews

The Applicants appreciate the courtesy extended by Examiners Welter and Channavajjala in conducting telephone interviews with the Applicants' representatives on January 06, 2009 and July 01, 2009. The Applicants hereby acknowledge the January 12, 2009 Interview Summary, which was mailed after the submission of the Applicants' previous reply, and the Interview Summary mailed July 07, 2009. During the July 01, 2009 interview, the Applicants' representatives reviewed with the Examiners the unexpected results regarding the bioequivalence of pioglitazone and metformin in the presently claimed preparations with respect to Actos® and Glucophage®, respectively. The Applicants' representatives also provided evidence showing that micronization of pioglitazone did not significantly affect the uniformity of the active pharmaceutical ingredients. Applicants further discussed the possibility of amending the present claims in concordance with the claims that were allowed in the Japanese counterpart application, which Applicants have done by way of the above amendments. The Examiners suggested that the Applicants file an RCE and submit the unexpected results via a Rule 132 Declaration.

II. Status of the Claims

Independent claims 15 and 24 are amended to recite that the median size of the particles of pioglitazone or a salt thereof is 2-10 μm. Support for the amendment can be found in, for example, lines 1-2 on page 6 of the Specification as-filed. Claim 15 is also combined with claim 18 to recite a specific embodiment of biguanide wherein the biguanide is metformin or a salt thereof. Claim 18 is cancelled and claim 19 is amended accordingly for its dependency. Further amendments are made to claims 20 and 25 to clarify the claimed invention. No new matter is introduced, and claims 15-25 are currently pending to be examined on their merits.

III. Claim Rejections – 35 U.S.C. § 103

Claims 15-21, 23, and 25 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Piper (WO 01/32158) in view of Zhuang (*Practical Pharm. Prep. Tech.*, January 1999, p203-04), as evidenced by Remington (*Remington: The Science and Practice of Pharmacy*, 21st Edition, 2003, pp. 675-676) and RxList: the Internet Drug List (http://www.rxlist.com/actos-drug.htm). Claims 22 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Piper in view of Zhuang, as evidenced by Remington and RxList and Kumar (US 6,117,451). The Applicants respectfully traverse these rejections.

Current Obviousness Standard

The U.S. Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a) and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., slip op. at 14 (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

Present claims are not obvious over prior art

While not acquiescing to the grounds of the rejections, independent claims 15 and 24 are amended to recite that the particles of pioglitazone or salt thereof have a median size of **2-10 μm**. Claim 15 is also amended to parallel claim 24, reciting that the biguanide is metformin or a salt thereof – the recitation of metformin or a salt thereof in claim 15 further supports that the unexpected properties as described below can only be obtained by the presently claimed preparations. The Office acknowledges that Piper does not teach or suggest a median particle size of metformin of 10-100 μm or a ratio of median size of the metformin particles to that of pioglitazone particles of 0.5 to 15. However, the Office asserts that it would be obvious to one of ordinary skill in the art to combine Piper's teaching with the pulverizing and/or sieving of Zhuang to reach the presently claimed preparations. The Applicants respectfully submit that, on the contrary, one of ordinary skill in the art would not have a reason to combine the teachings of Piper and Zhuang (*see KSR Int'l Co.*), and even if they were combined, any possible case of *prima facie* obviousness would be readily rebutted by the unexpected properties described below.

The presently claimed preparations exhibit unexpected properties that make the presently claimed preparations particularly suitable as an anti-diabetic combination drug. Specifically, as demonstrated in Mr. Masahiko Koike's Rule 132 Declaration, bioequivalence for both of the two active ingredients (pioglitazone and metformin) in a combination drug can only be achieved when the particle size of the pioglitazone has a median size of less than 10 μm, specifically 2-10 μm, as recited in claims 15 and 24.

The Koike Declaration demonstrates that while equivalence can be achieved between pioglitazone in a combination drug and that in Actos®, which contains pioglitazone as the only active ingredient, in an *in vitro* dissolution test, bioequivalence of pioglitazone can **only** be achieved in a human body during clinical studies if the particles of the pioglitazone are "**micronized**" – i.e., the median size of the pioglitazone particles was reduced to **less than 10**

μm, specifically between 2-10 μm, as recited in claims 15 and 24. **Such a discrepancy, as explained in the Koike Declaration, can be attributed to an unexpected *in vivo* drug interaction between the two active ingredients taking place in a human body, which is not only rare but also unpredictable to one of ordinary skill in the art**.

The Koike Declaration demonstrates that, by micronizing the pioglitazone particles in the presently claimed preparations, the present inventors have overcome the difficulties previously encountered in the prior art and produced a single-phase solid preparation, in which **both** the pioglitazone and metformin exhibit bioequivalence. The method commonly employed in the art to achieve bioequivalence for two active ingredients in a combined drug prior to the present application filing had been to produce a bilayer laminate preparation with one ingredient independently contained in each of the two layers. One challenge of the bilayer configuration is that in the case of containing a high dosage, the preparation is large and thus very difficult for a patient to swallow, resulting in patient discomfort. By contrast, the presently claimed invention provides a single-phase solid preparation (as opposed to a two-layer structure, thereby allowing the presently claimed preparation to be smaller in size than a bilayer preparation), which at the same time allows both active ingredients to achieve bioequivalence. **Even more surprisingly, the Koike Declaration shows that the micronization of the pioglitazone particles did not significantly affect the uniformity of either of the active ingredients, contrary to the suggestion in the outstanding Office Action that one of ordinary skill in the art would have micronized pioglitazone for the purpose of increasing uniformity**.

One of ordinary skill in the art would not have expected the complex and unpredictable drug-drug interaction *in vivo* described above. No combination of the cited references, Piper and/or Zhuang, teaches or suggests that the lack of bioequivalence encountered when these drugs are combined could be overcome by a preparation featuring the selected combination of features recited in independent claims 15 and 24. Thus, the teachings of Piper and Zhuang, alone or in combination, do not render the present claims obvious.

None of Remington, RxList, and Kumar remedies the deficiencies described above. The unexpected results set forth above overcome any possible case of *prima facie* obviousness.

Therefore, at least in view of the foregoing, the Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

The Applicants believe that the present application is now in condition for allowance and thus respectfully request favorable reconsideration of the application.

The Office is invited to contact the undersigned by telephone if a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing or a credit card payment form being unsigned, providing incorrect information resulting in a rejected credit card transaction, or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date July 24, 2009

By _____

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for the Applicants
Registration No. 35,264